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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/669,187	09/25/2000	Arthur M. Krieg	C1039/7035 (HCL/MAT)	2999

7590 05/15/2007

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EXAMINER	
BLANCHARD, DAVID J	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
05/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/669,187	KRIEG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-120 are cancelled.

2. Claim 121 has been amended.

Claims 139-142 have been added.

3. Claims 121-142 are under consideration.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

6. The objection to claim 121 as being an improper Markush-type is withdrawn in view of the amendments to the claim.

7. The rejection of claims 121-138 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation "one or more of carboplatin, paclitaxel, cisplatin, 5-fluorouracil, doxorubicin, taxol and gemcitabine..." in claim 121 is withdrawn in view of the amendments to the claim.

8. The rejection of claim 121 under 35 U.S.C. 112, second paragraph, as containing the trademark/trade name Taxol™ is withdrawn in view of the amendment to the claim.

9. The rejection of claims 121-130 under 35 U.S.C. 102(e) as being anticipated by Wagner et al (US 2004/0235778 A1, 5/14/1998) is withdrawn in view of the amendments to the claims.

Response to Arguments and New Grounds of Rejections

10. The rejection of claims 121-124, 128-132 and now applied to newly added claims 139-142 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer in a subject comprising administering the unmethylated immunostimulatory oligonucleotide of SEQ ID NO:246 comprising a modified backbone and a chemotherapeutic agent, does not reasonably provide

enablement for a method of treating cancer in a subject comprising administering the immunostimulatory oligonucleotide of SEQ ID NO:246 and a chemotherapeutic agent, wherein the oligonucleotide is unmethylated and lacks a phosphate backbone modification is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The response filed 2/12/2007 summarizes the factors used in the Wands analysis and argues that the claimed oligonucleotides may be rendered resistant to degradation by modifications to the backbone and by increasing the length of the oligonucleotide. Applicant states that oligonucleotides having native, unmodified backbones are immunostimulatory, and that oligonucleotides with stabilizing backbone modifications possessed longer half-lives due to resistance from endogenous nucleases and the ability to make and use such oligonucleotides was also known. Applicant refers to the previously submitted data (filed 6/15/2006) from human clinical trials showing the enhancing effect of SEQ ID NO:246 (i.e., unmethylated and having a phosphorothioate modified backbone), when used in combination with *carboplatin and paclitaxel* in the treatment of non-small cell lung cancer. Applicant asserts that sufficient therapeutic immunostimulatory activity is imparted by the core consensus sequence of SEQ ID NO:246 and practicing the claimed method does not require identification of additional nucleotides or sequences. Applicants' arguments have been fully considered but are not found persuasive. The claims are drawn to a method for increasing responsiveness to a cancer therapy, i.e., chemotherapy, comprising administering to a subject having cancer an immunostimulatory oligonucleotide comprising a nucleotide sequence of SEQ ID NO:246, which is interpreted to require only the nucleotide sequence, or even a fragment of SEQ ID NO:246, which would be "a nucleotide sequence" of SEQ ID NO:246. The fact that the claims merely require a nucleotide sequence of SEQ ID NO:246 and not SEQ ID NO:246 *per se* (disclosed as being unmethylated and having a phosphorothioate modified backbone), is particularly evident in view of dependent claims 125-127 and 133-135, which recite backbone modifications of SEQ ID NO:246, meaning that the base claims encompass SEQ ID NO:246 without a backbone

modification under the presumption that the dependent claims are further limiting. SEQ ID NO:246 is only disclosed as being unmethylated and containing a phosphorothioate backbone, thus, there is no description, guidance or direction for using SEQ ID NO:246 that is methylated and lacks a backbone modification as broadly encompassed by the claims and wherein SEQ ID NO:246 "comprises" additional sequence up to 40 or 100 nucleotides in length. While applicant refers to alternative ways in which the claimed immunostimulatory oligonucleotide may be protected from endogenous nucleases, such as increased length (i.e., "comprising a nucleotide sequence of SEQ ID NO:246", "up to 100 nucleotides in length" and "24-40 nucleotides in length"), the teachings, exemplification and clinical data referred to by applicant are limited to the administration of SEQ ID NO:246 (i.e., consisting of SEQ ID NO:246, which is unmethylated and comprises a phosphorothioate modified backbone) and a chemotherapeutic agent. Neither applicants arguments nor evidence provide a basis for the broader scope of the claims encompassing SEQ ID NO:246, as well as immunostimulatory oligonucleotides that "comprise" a nucleotide sequence of SEQ ID NO:246 (i.e., up to 40 or up to 100 nucleotides in length) that are unmethylated and do not contain a modified backbone. There is no basis or objective evidence that the inclusion of additional nucleotides or sequences to SEQ ID NO:246 would function equivalently, particularly in view of the prior art and applicants' specification which show that both length and nucleotide content are factors in determing the immunostimulatory properties of a given CpG oligonucleotide Thus, contrary to applicants assertion that the claimed method does require identification of additional nucleotides or sequences and their effect, if any, on the activity of SEQ ID NO:246, particularly when used in combination with the claimed chemotherapeutic agents. The issue is make and use, not make and test to see if the skilled artisan could use. The specification does not enable the genus because where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical

elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one particular species, what other species will work. See MPEP 2164.03.

The state of the art is such that using SEQ ID NO:246 that is methylated and lacks a backbone modification in the claimed methods would have been unpredictable. With respect to the art of Krieg et al (of record), applicant states that the claimed method recites an oligonucleotide having at least four CG dinucleotides with unmethylated cytosines, which the examiner has already acknowledged as being enabled. As discussed supra, the claims merely require a nucleotide sequence of SEQ ID NO:246, but not SEQ ID NO:246, *per se*, which is only disclosed as being unmethylated and having a phosphorothioate modified backbone. It is reiterated that the claims encompass SEQ ID NO:246 regardless of its methylation status and as such encompass methylated SEQ ID NO:246, which would be unpredictable in view of Krieg et al and Agrawal. Krieg teaches that when methylated, the CpG lost its immune stimulatory activity (pg. 342, first par.). Similarly, Agrawal et al. (Trends in Mol. Med, 8:114-121, 2002, of record) teaches, "The presence of unmethylated CpG dinucleotide is essential for the induction of immunostimulatory activity..." (See pg. 114, bottom of second column). Applicant has not presented any evidence that methylated SEQ ID NO:246 in combination with the claimed chemotherapeutic agents would function as unmethylated SEQ ID NO:246 as shown in the clinical data. Again, applicant is relying on the disclosure and showing of the immunostimulatory oligonucleotide "consisting" of SEQ ID NO:246, which is unmethylated and comprises a phosphorothioate modification to enable the claimed therapeutic method in cancer subjects comprising the administration of an immunostimulatory oligonucleotide "comprising" a nucleotide sequence of SEQ ID NO:246 (i.e., a fragment of SEQ ID NO:246 and comprising additional sequence in addition to SEQ ID NO:246 up to 40 or 100 nucleotides in length), that may be methylated and lacks a phosphate backbone modification that protects against nuclease degradation *in vivo*.

Amending the claims to recite administering the immunostimulatory oligonucleotide of SEQ ID NO:246 would overcome this rejection, given that SEQ ID NO:246 as set forth by the written description in the present application is unmethylated and comprises a phosphorothioate backbone. Applicant is reminded that such an amendment would also require amending claims 125-127 and 133-135 since a claim in a dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers and must further limit the subject matter claimed.

11. The rejection of claims 121-138 and now applied to newly added claims 139-142 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement as introducing new matter is maintained. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The response filed 2/12/2007 acknowledges that the claims are drawn to a genus of oligonucleotides that comprise the nucleotide sequence of SEQ ID NO:246, which is highlighted in the specification as being highly immunostimulatory. The genus of oligonucleotides is defined by the common consensus sequence of SEQ ID NO:246 and one of skill in the art could envision additional species within the recited genus based on the teaching in the specification. Applicants' arguments have been fully considered but are not found persuasive. As set forth in the previous Office Action and acknowledged by applicant, the claims encompass an extremely large genus of immunostimulatory oligonucleotides that comprise the consensus sequence of SEQ ID NO:246 and may contain additional sequence up to 40 or up to 100 nucleotides in length of the claimed method. However, written description of the present application only reasonably conveys a single immunostimulatory oligonucleotide "consisting" of SEQ ID NO:246. Applicants' reliance on the description of a single species of immunostimulatory oligonucleotide, SEQ ID NO:246, and having the properties and characteristics unique SEQ ID NO:246 is not representative of the entire genus because the genus is highly variable, inclusive to immunostimulatory oligonucleotides of varying lengths and having

different chemical structures or sequences, which were not clearly disclosed in the as filed application. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). There is insufficient written description for the subgenus of immunostimulatory oligonucleotides "comprising" up to 100 nucleotides or "comprising" 24-40 nucleotides as the as filed disclosure contains no description of the sequences contained therein and based on the limited disclosure of SEQ ID NO:246, one of skill in the art would reasonably conclude that the disclosure does not provide a representative number of species to describe the presently claimed sub-genus. Additionally, the as filed specification only discloses SEQ ID NO:246 as unmethylated and having a phosphorothioate backbone modification. Applicants reliance on a general disclosure and possibly a single species (i.e., phosphorothioate immunostimulatory oligonucleotide SEQ ID NO:246) has not provided sufficient direction and guidance to the features currently claimed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05. Further, Applicants' argument that one of skill in the art could envision additional species within the recited genus based on the teaching in the specification seems to go more toward enablement than description. That is, the argument seems intended to show that, following the teachings in the specification, those skilled in the art could have produced other immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246, and determined which (if any) would function equivalently, without undue experimentation. The instant rejection is based on lack of adequate written description,

not lack of enablement. The written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Applicant also argues that the claimed combination of the immunostimulatory oligonucleotide and the claimed chemotherapeutic agents are adequately supported on pp. 15-16. Applicant also asserts that the claimed chemotherapeutics represent the standard of care for treatment of non-small-cell lung cancer and applicant provides a review article fro chemotherapy regimens in non-small-cell lung cancer (Schiller et al, NEJM, 346, p. 92, 2002). Applicant also argues the relevancy of the case law cited by the examiner in the previous Office Action. Applicants' arguments have been fully considered but are not found persuasive. The disclosure at pp. 15-16 of the specification of every possible chemotherapeutic agent as being used in combination with an immunostimulatory oligonucleotide does not provide adequate direction or guidance to the currently claimed limitations. There is nothing in the general disclosure of the numerous immunostimulatory oligonucleotides (e.g., see Table A) and the numerous chemotherapeutic agents listed at pp. 15-16 as pointed to by applicant that would have led the skilled artisan to the claimed combination of SEQ ID NO:246 or the subgenus of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 in combination with carboplatin, *carboplatin and paclitaxel*, paclitaxel, doxorubicin, cisplatin, or gemcitabine for the treatment of cancer as opposed to the selection of any of the other possible combinations of chemotherapeutic agents, immunotherapeutic agents or cancer vaccines. Further, where in the as filed disclosure is it contemplated that *carboplatin and paclitaxel* was the intended combination of chemotherapeutic agents to be used with SEQ ID NO:246 in the treatment of non-small cell lung cancer? The examiner agrees with applicant that the specific facts in the cited case law differ from the facts in the present application, however, the findings are not and are relevant to the instant rejection. As discussed supra and similar to *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996), a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a

genus because it would not "reasonably lead" those skilled in the art to any particular species. Similarly, the laundry list of immunostimulatory oligonucleotides in Table A and elsewhere in the specification and the laundry list of chemotherapeutic agents that extend well beyond the few claimed would not have "reasonably led" those skilled in the art to the particular claimed combinations presently claimed. This is also similar to the findings in *In re Ruschig*, in which the court stated: it is our considered opinion that the board was correct in saying:

> "Not having been specifically named or mentioned in any manner, one is left to selection from the myriads of possibilities encompassed by the broad disclosure, with no guide indicating or directing that this particular selection should be made rather than any of the many others which could also be made." (see. pg. 123).

Similarly, the present application does not name or describe the subgenus of immunostimulatory sequences that "comprise" SEQ ID NO:246, or the particular combinations of said sequences and carboplatin, *carboplatin and paclitaxel*, paclitaxel, doxorubicin, cisplatin, or gemcitabine as presently claimed from the myriad of possibilities encompassed by the broad disclosure (e.g., Table A and pp. 15-16) and there is no guidance or direction that the particular combinations presently claimed should be made rather than any of the others which could also be made. While the specifics in Martin v. Mayer focused on "wires" and "cables", as summarized in Martin v. Mayer, [I]t is "not a question of whether one skilled in the art might be able to construct the patentee's device from the teachings of the disclosure . . . . Rather, it is a question whether the application necessarily discloses that particular device.", which is relevant to the present case which does not adequately disclose the particular combinations presently claimed as discussed supra. Similar to I*n re Smith*, the present claims are drawn to a various subgenus's of immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 and a particular chemotherapeutic agent(s), which are not adequately supported or described in applicants' generic disclosure of an immunostimulatory oligonucleotide in combination with a chemotherapeutic agent, an immunotherapeutic agent, or a cancer vaccine (e.g., see pp. 15-16), or in the disclosure of a single species, i.e., SEQ ID NO:246. Applicants' reliance on a generic disclosure (i.e., an

immunostimulatory oligonucleotide in combination with a chemotherapeutic agent, an immunotherapeutic agent or a cancer vaccine) and possibly a single species (i.e., SEQ ID NO:246) has not provided sufficient direction and guidance to the features currently claimed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See *In re Smith* 173 USPQ 679, 683 (CCPA 1972); *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971).

For these reasons and those already of record the rejection is maintained.

12. The rejection of claims 121-138 and now applied to newly added claims 139-142 under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (US 2004/0235778 A1, 5/14/1998) in view of Maxwell et al (Seminars in Oncology Nursing, 8(2):113-123, May 1992) is maintained.

The response filed 2/12/2007 sates that claim 121 has been amended to recite administration of carboplatin and paclitaxel and the cited references do not teach that SEQ ID NO:246 should be administered to treat non-small cell lung cancer with the chemotherapeutic agents carboplatin and paclitaxel. Applicant states that this combination produces a synergistic result that was unexpected and not foreseen by the disclosures of Maxwell and Wagner. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., SEQ ID NO:246 should be administered to treat non-small cell lung cancer with the chemotherapeutic agents carboplatin and paclitaxel), with the exception of claim 131, are not recited in the rejected claims. Applicant's assertion of synergy, and evidence of unexpected results in the previous response (filed 6/15/2006) are not supported by Manegold et al. Table 2 of Manegold shows that the combination of SEQ ID NO:246 (i.e., "PF-3512676") in combination with paclitaxel and carboplatin had a 36% response rate whereas chemotherapy alone resulted in a response rate of 49%. Further, the scope of the claims encompasses immunostimulatory oligonucleotides that "comprise" SEQ ID NO:246 and do not require SEQ ID NO:246 in combination with carboplatin and paclitaxel. Additionally, in view of the data provided in Table 2 of Manegold, one of ordinary skill in the art would not be

able to determine a trend in the exemplified data to support the nonobviousness of the broader scope of the claims. The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data, which would allow the artisan to reasonably extend the probative value thereof. *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references and the rejection is maintained.

13. No claims are allowed.

14. . Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Blanchard
Primary Examiner
Art Unit 1643

DB
May 10, 2007